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PUBLISHED INTERNATIONAL APPLICATION

(11) **WO 98/54315** (13) A1

(21) PCT/US98/10001

(22) **15 May 1998 (15.05.1998)**

(25) ENG (26) ENG

(31) 08/867,230 (32) **30 May 1997 (30.05.1997)** (33) US

(43) 03 December 1998 (03.12.1998)

(51)[6] C12N 15/11, A61K 31/70

(54) CELL GROWTH-CONTROLLING OLIGONUCLEOTIDES

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(81) CA, JP ; EP (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE)

No Image Available.

Abstract

The present invention provides a partial cDNA corresponding to an RNA containing double stranded regions (R-RNA), which, when transcribed in vitro , gives rise to an RNA transcript that activates PKR. An approximately 226-252 bp nucleotide (nt) sequence responsible for activation of PKR (the activation sequence) has been identified within the cDNA and isolated. Antisense oligonucleotides corresponding to specific portions of the 252 nt cDNA fragment stimulate proliferation of different cells in culture. Various portions of the cDNA or R-RNA may also be used to inhibit cell proliferation in cell cultures. The present invention further provides pharmaceutical compositions comprising the subject nucleic acid fragments and oligonucleotides. Kits which comprise at least one of the subject isolated nucleic acid molecules or oligonucleotides and a pharmaceutically acceptable carrier are also provided.

Presentation: Basic Image: Sma Français

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1: Curr Biol 2003 Jan 8;13(1):41-6

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Short-Interfering-RNA-Mediated Gene Silencing in Mammalian Cells Requires Dicer and eIF2C Translation Initiation Factors.

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RNA interference (RNAi) is the process of long, double-stranded (ds), RNA-dependent posttranscriptional gene silencing (PTGS). In lower eukaryotes, dsRNA introduced into the cytoplasm is cleaved by the RNaseIII-like enzyme, Dicer, to 21-23 nt RNA (short interfering [si] RNA), which may serve as guide for target mRNA degradation. In mammals, long-dsRNA-dependent PTGS is applicable only to a limited number of cell types, whereas siRNA synthesized in vitro is capable of effectively inducing gene silencing in a wide variety of cells. Although biochemical and genetic analyses in lower eukaryotes showed that Dicer and some PIWI family member proteins are essential for long-dsRNA-dependent PTGS, little is known about the molecular mechanisms underlying siRNA-based PTGS. Here, we show that Dicer and eIF2C translation initiation factors belonging to the PIWI family (eIF2C1-4) play an essential role in mammalian siRNA-mediated PTGS, most probably through synergistic interactions. Immunoprecipitation experiments suggest that, in human and mouse cells, complex formation occurs between Dicer and eIF2C1 or 2 and that the PIWI domain of eIF2C is essential for the formation of this complex.

PMID: 12526743 [PubMed - in process]

1: J Interferon Res 1993 Apr;13(2):153-60

Inhibition of the dsRNA-dependent protein kinase by a peptide derived from the human immunodeficiency virus type 1 Tat protein.

Judware R, Li J, Petryshyn R.

Department of Biochemistry and Molecular Biology, State University of New York, Syracuse 13210.

The human immunodeficiency virus (HIV) is the etiologic agent leading to the development of acquired immunodeficiency syndrome (AIDS). Interferons (IFNs) are known for eliciting antiviral responses from cells, and studies have indicated that infection with HIV induces the production of IFN. Previous studies have shown that the trans-acting response element (TAR) sequence of HIV-1 mRNA can activate the IFN-induced double-stranded (ds) RNA-dependent protein kinase (DAI). DAI, when activated, is a potent inhibitor of protein synthesis and has been implicated in mediating part of IFN's antiviral activity. Here, we report that a synthetic peptide containing the basic region of HIV Tat protein is effective in preventing the activation of DAI. Evidence is presented that indicates that the Tat peptide exerts its effect by binding to the TAR RNA sequence and thus preventing this RNA from binding to and activating DAI. It appears that in addition to its role in trans-activation, the tat protein may also function to overcome the antiviral activity of IFN by regulating DAI activity. Thus, inhibition of DAI by the Tat protein early in the life cycle of HIV may provide a mechanism by which the virus can escape a translational block imposed by the kinase.

PMID: 8099600 [PubMed - indexed for MEDLINE]

1: Virology 1996 Aug 1;222(1):193-200

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Peptides derived from the interferon-induced PKR prevent activation by HIV-1 TAR RNA.

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The double-stranded RNA-dependent protein kinase (PKR) is believed to mediate cellular antiviral responses, function as a tumor suppressor, and regulate cell growth and differentiation. Its activation is dependent on double-stranded RNA (dsRNA) structures but these interactions are not fully understood. The possibility of direct interaction between dsRNA and the arginine and lysine-rich region of PKR (residues 54-74) was examined using synthetic peptides. We found that addition of a synthetic peptide corresponding to residues 54-74 of murine PKR or residues 60-80 of human PKR inhibited the autophosphorylation and activation of the kinase by either poly(I)-poly(C) or the 82-nucleotide-long TAR RNA. Gel-shift analysis indicated that the peptides disrupted the kinase-TAR complex by binding directly to TAR RNA. These findings delineate at least one dsRNA-binding domain in PKR which may be important for its cellular activation.

PMID: 8806499 [PubMed - indexed for MEDLINE]

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PUBLISHED INTERNATIONAL APPLICATION

(11) **WO 98/04717** (13) A2

(21) PCT/US97/14350

(22) **29 July 1997 (29.07.1997)**

(25) ENG (26) ENG

(31) 60/023,307 (32) **30 July 1996 (30.07.1996)** (33) US

(43) 05 February 1998 (05.02.1998)

(51)[6] C12N 15/54, 15/85, 9/12, 5/10, C12Q 1/68, C07K 16/40, A61K 38/45, 39/395, G01N 33/50

(54) DOUBLE-STRANDED RNA DEPENDENT PROTEIN KINASE DERIVED PEPTIDES TO PROMOTE PROLIFERATION OF CELLS AND TISSUES IN A CONTROLLED MANNER

(71) **THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** Bethesda, MD 20892 ; (US). [US/US]. *(for all designated states except US)*

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(81) AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU ; AP (GH, KE, LS, MW, SD, SZ, UG, ZW); EA (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); EP (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE); OA (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG)

No Image Available.

Abstract

This invention relates to double-stranded RNA dependent protein kinase (PKR) peptide antagonists. More specifically, the invention relates to compositions and methods for antagonizing activation of double-stranded RNA dependent protein kinase (PKR) to stimulate eukaryotic cell proliferation. The invention relates to compositions and methods to inhibit activation of double-stranded RNA dependent protein kinase (PKR) to stimulate cell proliferation under conditions of cell cycle arrest, quiescence, reduced growth or cell death. The invention also relates to methods of protecting cells from HIV-1 pathogenesis using inhibitors of PKR.